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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,152	06/21/2000	David J. Yang	UTXC:664	6919

7590

09/29/2003

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EXAMINER

JONES, DAMERON LEVEST

ART UNIT

PAPER NUMBER

1616

DATE MAILED: 09/29/2003

22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/599,152

Applicant(s)

YANG ET AL.

Examiner

D. L. Jones

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-4,6-35,37-41 and 52-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-4,6,8-10,15,20,23,30-35 and 37-41 is/are rejected.
- 7) ☒ Claim(s) 7,11-14,16-19,21,22,24-29 and 52-55 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 20. 6) ☐ Other:

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of the following: (a) Paper No. 17, filed 7/22/03, wherein an acceptable RCE was filed; (b) Paper No. 18, filed 7/22/03, wherein claims 5 and 36 were canceled and claims 6, 8, 10, 15, 21, 23, 33, 35, 37, and 38 were amended; and (c) Paper No. 19, filed 7/22/03, wherein a declaration by Yang, Liu, Yu, and Kim were submitted.

Note: Claims 2-4, 6-35, 37-41, and 52-55 are pending.

RESPONSE TO APPLICANT'S ARGUMENTS/AMENDMENT

2. The Applicant's arguments filed 7/22/03 (Paper No. 18) to the rejection of claims 2-5 and 33-38 made by the Examiner under 35 USC 103 have been fully considered and deemed persuasive. Therefore, all outstanding rejections are hereby withdrawn.

NEW GROUNDS OF REJECTION

112 First Paragraph Rejection

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of synthesizing a radiolabeled ethylenedicysteine (EC) complex wherein the tissue specific ligand is selected from (a) anticancer agents methotrexate, doxorubicin,

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tamoxifen, paclitaxel, topotecan, LHRH, mitomycin C, etoposide, tomudex, podophyllotoxin, mitoxantrone, camptothecin, colchicines, endostatin, fludarabin, and gemcitabine; (b) tumor markers PSA, ER, PR, CA-125, CA-199, CEA, AFP, interferon, BRCA1, HER-2/neu, cytoxan, p53, and endostatin; (c) folate receptor targeting agents folate, methotrexate, folic acid, and tomudex; (d) tumor apoptotic cell targeting ligands and tumor hypoxia targeting agents annexin V, nitroimidazole, mitomycin, colchicine, and metronidazole; (e) glutamate pentapeptide; (f) glucose mimics neomycin, kanamycin, entamycin, paromycin, amikacin, tobramycin, netilmicin, ribostamycin, sisomicin, micromicin, lividomycin, dibekacin, isepamicin, astromicin, glucosamine, and aminoglycoside; and (g) glucose, does not reasonably provide enablement for all tissue specific agents wherein the agents are anticancer agents, tumor markers, folate receptor targeting ligands, tumor apoptotic cell targeting ligands, tumor hypoxia targeting ligands, or agents that mimic glucose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are several guidelines when determining if the specification of an application allows the skilled artisan to practice the invention without undue experimentation. The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are (1) nature of the invention; (2) state of the prior art; (3) level of one of ordinary skill in the art; (4) level of predictability in the art; (5) amount of direction and guidance provided by the inventor; (6) existence of working examples; (7)

breadth of claims; and (8) quantity of experimentation needed to make or use the invention based on the content of the disclosure.

(1) Nature of the invention

The claims are directed to methods of synthesizing EC-tissue specific ligand complexes comprising binding a tissue specific ligands selected from anticancer agents, tumor markers, folate receptor targeting ligands, tumor apoptotic cell targeting ligands, tumor hypoxia targeting ligands, or agents that mimic glucose, or glutamate pentapeptide to EC .

(2) State of the prior art

The prior art references of record do not indicate which anticancer agents, tumor markers, folate receptor targeting ligands, tumor apoptotic cell targeting ligands, tumor hypoxia targeting ligands, or agents that mimic glucose are useful in the claimed invention. Applicant discloses various references throughout the specification that pertain to EC synthesis. The radiolabeling of EC (and uses thereof) wherein the ligand is conjugated to specific anticancer agents, tumor markers, folate receptor targeting ligands, tumor apoptotic cell targeting ligands, tumor hypoxia targeting ligands, or agents that mimic glucose is not disclosed in the art. It should be note that the novelty of the instant invention is not the synthesizing of radiolabeled EC, but the radiolabeling of specific tissue specific ligands with EC.

(3) Level of one of ordinary skill in the art

The level of one of ordinary skill in the art is high. The specific targeting agents encompassed in Applicant's independent claims encompass a vast number of possible

compounds. Applicant's specification does not enable the public to make or use such a vast number of EC-targeting agent complexes as set forth in the instant invention.

(4) Level of predictability in the art

The art pertaining to synthesizing EC conjugated to various targeting agents is highly unpredictable. For example, determining the various types of targeting agents or classes of agents that will bind to EC and generate results (i.e., imaging quality, stability, etc.) consistent with that obtainable by Applicant requires various experimental procedures and without guidance that enables a skilled practitioner to select specific targeting agents and not others, there would be little predictability in performing the claimed invention.

(5) Amount of direction and guidance provided by the inventor

Applicant's independent claims encompass a vast number of tissue specific ligands. Applicant's limited guidance does not enable the public to prepare such a numerous amount of EC-targeting agent combinations. There is no directional guidance for the specific targeting agents that will generate results consistent with those obtained by Applicant when bound to EC, especially since, according to prior art cited previously, Anderson et al (Nucl. Med. Biol., 1995, Vol. 22, No. 2, pages 165-173), it is well known in the art to generate radiolabeled EC-complexes. Hence, there is no enablement for all possible permutations and combinations of the EC-targeting agents.

(6) Existence of working examples

Applicant's independent claims encompass a vast number of EC-targeting agent complexes. Applicant's limited working examples do not enable the public to prepare

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such a numerous amount of EC-targeting agent combinations. While Applicant's claims encompass a plethora of possible combinations, the specification provides support for the following EC-targeting agents: methotrexate, doxorubicin, tamoxifen, paclitaxel, topotecan, LHRH, mitomycin C, etoposide, tomudex, podophyllotoxin, mitoxantrone, camptothecin, colchicines, endostatin, fludarabin, gemcitabine, PSA, ER, PR, CA-125, CA-199, CEA, AFP, interferon, BRCA1, HER-2/neu, cytoxan, p53, endostatin, folate, methotrexate, folic acid, tomudex, annexin V, nitroimidazole, mitomycin, colchicine, metronidazole, glutamate pentapeptide, neomycin, kanamycin, entamycin, paromycin, amikacin, tobramycin, netilmicin, ribostamycin, sisomicin, micromicin, lividomycin, dibekacin, isepamicin, astromicin, aminoglycoside, glucosamine, and glucose.

(7) Breadth of claims

The claims are extremely broad due to the vast number of possible EC-targeting agent combinations.

(8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

The specification does not enable any person skilled in the art to which it pertains to make or use the invention commensurate in scope with the claims. In particular, the specification fails to enable the skilled artisan to practice the invention without undue experimentation as it relates to selecting the various targeting agents. Furthermore, based on the unpredictable nature of the invention, the state of the prior art, and the extreme breadth of the claims, one skilled in the art could not perform the claimed invention without undue experimentation.

112 Second Paragraph Rejection

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2-4, 6, 8-10, 15, 20, 23, 30-35, and 37-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9: The claim as written is confusing because of the tissue specific ligands of claim 9, specifically, a monoclonal antibody or an antisense are not encompassed in the tissue specific ligands of independent claim 33. It is noted that the independent claims were amended to remove the tissue specific ligand, 'antibody' from the list of possible ligands.

Claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41: The claims as written are ambiguous because one cannot readily ascertain what is being claimed. Specifically, the claims as written read on a multitude of EC-targeting agent combinations. However, one of ordinary skill in the art would not be able to ascertain what is encompassed in the claim as written since the number of targeting agents encompassed in Applicant's phrases 'anticancer agent', 'tumor marker', 'a folate receptor targeting ligand', 'a tumor apoptotic cell targeting ligand', 'a tumor hypoxia targeting ligand', and 'an agent that mimics glucose' are unlimited. Hence, Applicant is respectfully requested to clarify the claim in order that one may determine what is being claimed.

Claim 20: The claim as written is ambiguous because the species set forth in claim 20 is not consistent with that of dependent claim 16. Did Applicant intend to write 99mTc-EC-metronidazole?

Claim 32: The claim as written is confusing because the tissue specific ligands of independent claim 33 do not encompass estradiol, octreotide, or VIP. It is noted that prior art was previously cited against EC-peptide/protein complexes (Anderson et al, Nucl. Med. Biol., 1995, Vol. 22, No. 2, pages 165-173) and Applicant amended the claims to exclude that the tissue specific ligand is a general peptide. Thus, it is unclear whether Applicant intended to remove the terms.

CLAIM OBJECTIONS

7. Claims 7, 11-14, 16-19, 21, 22, 24-29, and 52-55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Note: The claims are distinguished over the cited prior art of record because the prior art neither anticipates nor renders obvious the specific targeting agents complexed with EC as set forth in the claims.

COMMENTS/NOTES

8. It should be noted that the claims as written may be considered as 'reach thru claims' because while Applicant is entitled to allowable subject matter in which they discovered, the claims encompass species in which Applicant had no knowledge of that


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may be radiolabeled with EC. As a result, the above 112 rejections are necessary in order to clearly set forth what is Applicant's invention.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.


D. L. Jones
Primary Examiner
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September 25, 2003